DFT design of inhibitors of the LPXC enzyme

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In recent years bacterial infections have become more resistant to treatments, posing a challenge for both researchers and health professionals. The enzyme LpxC is responsible for catalyzing the first committed step in the biosynthetic pathway of Lipid A, a component of the selectively permeable outer membrane of Gram-negative bacteria. The inhibition of LpxC would therefore, prevent the production of Lipid A, and hence result in a corrupted outer membrane. Starting from the LpxC crystal structure with a natural substrate bound in the active site (PDB ID 2IER), we have designed and optimized the position of several novel ligands in the active site. We have studied ligands for the whole active site, ligands without the uracil component, and ligands without the hydrophobic moiety. The structures for these ligand-protein complexes were optimized using m06l and the 6-31G basis set both with implicit solvation and relaxed amino acid residue side chains. Interaction energies for the ligand and protein complexes were calculated using m06l with the 6-311+G* basis set. Desolvation and simplified zinc binding studies have also been performed to confirm that our model chemistry describes the zinc binding in the protein appropriately. Initial work shows several promising candidates for the inhibition of LpxC.

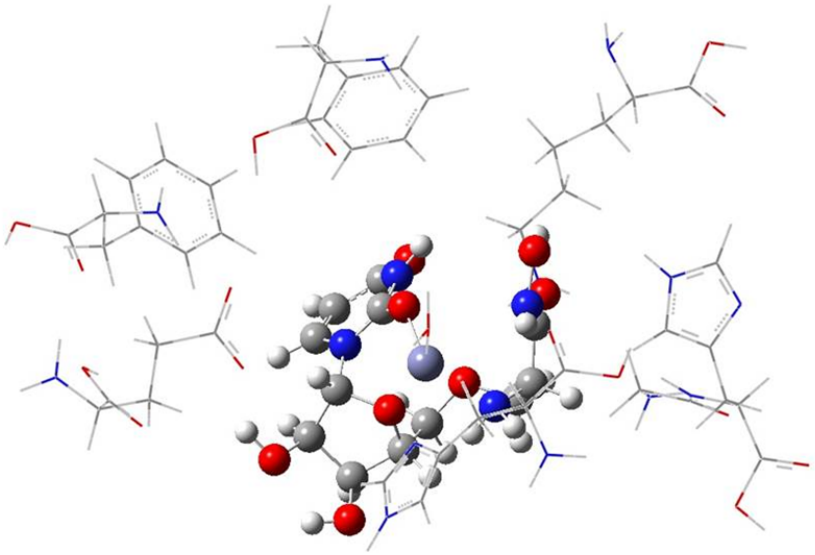

Figure One: Molecule SA-001 docked in the active site.